merits of this position, and in an effort to expedite prosecution, Applicants have amended claim 54 to be specifically drawn to the claims set forth by the Examiner, and thus claim 54 is now directed to the generation of antibodies from a peptide selected from the group consisting of SEQ ID NOS: 2, 4, 6, 10, 13, 17-20, 54-55, 57, 59-61, 86, 103 and 104.

In addition, in the Advisory Action, the Examiner noted that priority of the instant application has not been assigned to that of the priority document, namely the provisional document 60/036,139 since the Examiner found it not apparent that all claimed sequences were disclosed in the priority document. In accordance with the telephone interview of April 24, 2003, and in order to make this clear for the Examiner who apparently was having difficulty in tracking the source in the priority document of the sequences in the application, Applicants provide Appendix 1 which specifically correlates all claimed sequences in the present application with their source in the priority document, referring in each case to the specific page or figure and line number on said page or in said figure on which the present SEQ ID NO is found. In addition, the Applicants provide Appendix 2 which includes marked up pages of the specification, pages 100, 104 and 105, and Figures 10A, 10B, 11A and 11B, identifying various sequences in accordance with the request of the Examiner during the telephone interview.[1] Accordingly, the present application is entitled to its priority date for the subject matter disclosed in the priority application.

[1] As shown in the Appendix 1, all of the claimed sequences were disclosed with the exception of SEQ ID NO: 104. However, SEQ ID NO: 104 is also not disclosed or suggested in the cited Sun et al. article and thus this reference does not affect the patentability of the claims in any way.

The advisory action recognized that the prior amendment overcame the prior rejections under 35 U.S.C. § 112, and thus these rejections will not be further addressed.

As indicated in the advisory action, Claims 54-59 stand under 35 U.S.C. § 103(a) as being unpatentable over Sun et al (hereinafter "Sun"). However, as previously pointed out by Applicants, the Sun et al. article is substantially the same as Applicants' priority document and thus cannot be utilized in a rejection of the present claims. Moreover, as requested by the Examiner, a detailed Appendix is provided herewith which points out where each and every specific peptide sequence of the present claims (with the exception of SEQ ID NO:104; see above footnote) is supported in the priority document. Accordingly, the Sun et al. article cannot be used in a rejection of the present claims, and Applicants respectfully request that the rejection to claims 54-59 under 35 U.S.C. § 103(a) as being unpatentable over Sun be withdrawn.

In the advisory action and final rejection, Claims 54-59 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Hook et al WO 92/02555 (hereinafter "Hook '555"), with the Examiner alleging that Hook '555 discloses SEQ ID NO: 61 and 104, namely at the abstract and page 4, lines 16-36. This rejection is respectfully traversed.

Contrary to the Examiner's allegation, Hook '555 fails to teach or suggest the subject matter of Claim 54. In the first place, there is clearly no disclosure or suggestion of the presently claimed method, namely a method of generating an antibody that binds to a fibronectin binding domain of a fibronectin binding protein raised by administering to a human or animal a pharmaceutical composition comprising an immunologically effective amount of a peptide of a fibronectin binding domain of a fibronectin binding

protein that does **not** bind to fibronectin, a point that is conceded by the Examiner. However, the Examiner alleges that SEQ ID NO: 61 and 104 are disclosed in Hook '555 and that this inherently means that the invention is disclosed in that reference, and this is simply not the case. On the contrary, Hook '555 discloses in the abstract and on page 4, line 16 a sequence which is not identical with the sequences of SEQ ID NO: 61 and 104 which is easily observed by comparing the sequences. Accordingly, the specific peptides of SEQ ID's 61 and 104 are **not** disclosed in the Hook '555 patent, nor would be they be suggested or obvious in light of the Hook '555 reference because that reference nowhere discloses or suggests that one should look for and utilize peptides which themselves do **not** bind to fibronectin in order to generate antibodies that will be effective in inhibiting binding. Accordingly, the cited Hook '555 reference does not disclose or suggest the invention as presently claimed, and the Examiner's rejection on the basis of this reference is traversed and should be withdrawn.

Similarly, Claims 54-59 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hook et al U.S. Patent No. 5,440,014 (hereinafter "Hook '014"). Essentially, the Examiner argues that the same sequence as disclosed in the Hook '555 patent discloses the sequences of the invention and thus inherently anticipates or makes obvious the present invention. Contrary to the Examiner's assertions, for reasons as stated above, the precise sequence of the claimed peptides is **not** disclosed or suggested in Hook '014, and indeed this reference makes no disclosure or suggestion of the claimed invention in which a peptide that does not itself bind to fibronectin is utilized in generating antibodies that will be more effective in inhibiting the binding of the fibronectin binding protein to fibronectin in host cells. At most, the

reference discloses larger peptides of which the specific peptides of the claims are merely portions, and it is clear that antibodies generated from larger peptides will have potentially very different properties that smaller peptides contained therein. Accordingly, it is clear that the invention as presently claimed is not anticipated or made obvious by the Hook '014 patent, and the Examiner's rejection on the basis of this reference is respectfully traversed and should be withdrawn.

Finally, Claims 54-59 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Huff et al (hereinafter "Huff") based on the Examiner's incorrect statement that Huff discloses Applicants' sequences SEQ ID NO: 61 and 103. Once again, Huff does **not** disclose these specific sequences which is clearly shown based on a comparison of the exact sequences disclosed in Huff with the sequence 61 and 103 of the present claims. The mere fact that the sequences of Huff may include at various points Applicants' claimed sequences is of no relevance to the patentability of the present invention since it is the case that larger sequences which include additional amino acids typically generate antibodies with different properties, and thus the mere disclosure of sequences which include sequences claimed in the invention does not disclose or suggest the invention. Moreover, it is clear that the Huff reference does **not** disclose or suggest the present invention because it makes no mention or suggestion whatsoever of the key element of the present invention, namely the generation of antibodies from peptides from the fibronectin binding domain which do **not** themselves bind to fibronectin, which is a point that the Examiner has conceded. Accordingly, the Huff article does not disclose or suggest the present invention, and the rejection on the basis of this reference is respectfully traversed and should be withdrawn.

In light of the above amendments and arguments, it is respectfully submitted that the present application is now in condition for immediate allowance, and such action is earnestly solicited.

Respectfully submitted,
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June 3, 2003

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ATTACHMENT A

Marked Up Replacement Claim

Following herewith is a marked up copy of each rewritten claim.

54. (Currently amended) A method of generating an antibody that binds to a fibronectin binding domain of a fibronectin binding protein and inhibits binding of said fibronectin binding protein to fibronectin, comprising administering to a human or animal a pharmaceutical composition comprising an immunologically effective amount of a peptide of a fibronectin binding domain of a fibronectin binding protein that does not bind to fibronectin, wherein said peptide is selected from the group consisting of SEQ ID NOS: 2, 4, 6, 8, 10, ~~12-55,~~ 13, 17-20, 54-55, 57, ~~59-86, 88-105,~~ 59-61, 86, 103 and 104.

APPENDIX 1

Present Application 09/010,317 SEQ ID NO	Priority Document/ Provisional Application SEQ ID NO (if provided)	Page Number or Figure In The Priority Document/ Provisional Application 60/036,139
2	----	Fig. 10, line 24
4	56	88
6	39	88
8	47	88
10	15	82
12	51	85
13	15 (from D3-P)	88
14	9	82
15	10	82
16	11	82
17	12	82
18	13	82
19	14	82
20	16	82
21	17	82
22	18	82
23	19	82
24	20	82
25	21	82
26	22	82
27	23	82
28	24	82
29	25	82
30	26	82
31	27	82

32	28	82
33	29	82
34	59	82
35	31	83
36	32	83
37	33	83
38	34	83
39	35	83
40	36	83
41	37	83
42	38	83
43	40	83
44	41	83
45	43	84
46	44	84
47	45	84
48	46	84
49	48	84
50	49	84
51	52	85
52	53	85
53	54	85
54	55	85
55	58	85
57	42	84
59	47	Fig. 4A
60	----	100, line 10
61	----	100, line 11
62	----	104, line 4, second sequence
63	----	Fig. 10, line 1

64	----	Fig. 10, line 2
65	----	Fig. 10, line 3
66	----	Fig. 10, line 4
67	----	Fig. 10, line 5
68	----	Fig. 10, line 6 and Fig. 11, line 16
69	----	Fig. 10, line 7
70	----	Fig. 10, line 8
71	----	Fig. 10, line 9
72	----	Fig. 10, line 10
73	----	Fig. 10, line 11
74	----	Fig. 10, line 12 and Fig. 11, line 17
75	----	Fig. 10, line 13
76	----	Fig. 10, line 14
77	----	Fig. 10, line 15
78	----	Fig. 10, line 16
79	----	Fig. 10, line 17
80	----	Fig. 10, line 18
81	----	Fig. 10, line 19
82	----	Fig. 10, line 20
83	----	Fig. 10, line 21
84	----	Fig. 10, line 22
85	----	Fig. 10, line 23
86	----	101, line 24
88	----	Fig. 11, line 1
89	----	Fig. 11, line 2
90	----	Fig. 11, line 3
91	----	Fig. 11, line 4
92	----	Fig. 11, line 5

93	----	Fig. 11, line 6
94	----	Fig. 11, line 7
95	----	Fig. 11, line 8
96	----	Fig. 11, line 9
97	----	Fig. 11, line 10
98	----	Fig. 11, line 11
99	----	Fig. 11, line 12
100	----	Fig. 11, line 13
101	----	Fig. 11, line 14
102	----	Fig. 11, line 15
103	----	105, line 7
104	----	----
105	----	104, line 4 (first sequence)

ATTACHMENT B

Clean Replacement Claim

Following herewith is a clean copy of each claim which replaces each previous claim having the same number.

54. (Currently amended) A method of generating an antibody that binds to a fibronectin binding domain of a fibronectin binding protein and inhibits binding of said fibronectin binding protein to fibronectin, comprising administering to a human or animal a pharmaceutical composition comprising an immunologically effective amount of a peptide of a fibronectin binding domain of a fibronectin binding protein that does not bind to fibronectin, wherein said peptide is selected from the group consisting of SEQ ID NOS: 2, 4, 6, 8, 10, 13, 17-20, 54-55, 57, 59-61, 86, 103 and 104.

ammonium sulfate precipitation, followed by Q-Sepharose and Phenyl-Sepharose (Pharmacia) chromatography employing a Pharmacia Gradi-Frac chromatography system. For purification of antibodies, an affinity matrix was prepared by dissolving the lyophilized fusion protein in 0.5 M sodium bicarbonate (2 mg/ml), and adding an equal volume of carbonyldiimidazole-activated (Bethell *et al.* 1979) Sepharose CL4B (Pharmacia). After coupling for 48 h at 4°C with end-over-end mixing, assay of residual protein using the bicinchoninic acid protocol (Smith *et al.* 1985) established a coupling efficiency of 70%.

5.10.1.2 PREPARATION OF SYNTHETIC PEPTIDE ANTIGENS

Amino acids 21-34 of the D1 motif ($D1_{21-34}$; QGGNIVDIDFDSVP) and 20-33 of the D3 motif ($D3_{20-33}$; QFGGHNSVDFEEDT) were synthesized with an N-terminal cysteine by the University of Calgary Peptide Synthesis Core Facility, utilizing an Applied Biosystems model 431A peptide synthesizer. The peptides were coupled via the N-terminal cysteine to maleimide-activated Keyhole Limpet Hemocyanin (KLH) or bovine serum albumin (BSA) according to the protocols provided with the Imject Immunogen Conjugation kit (Pierce; Rockford, Ill).

5.10.1.3 PRODUCTION OF ANTISERA AND PURIFICATION OF ANTIBODIES

Six male New Zealand White rabbits were immunized subcutaneously with 1 mg of GSTD1-3 in Freunds complete adjuvant (Sigma). Groups of three rabbits were boosted at two week intervals by intramuscular injection of 80 µg of either GSTD1-3, or D1-3 peptide, in incomplete adjuvant. The animals were bled ten days after each immunization, and terminally bled by heart puncture after 128 days. For purification of antibodies, antisera was depleted of Fn by chromatography on gelatin Sepharose (Miekka *et al.* 1982), then passed over an affinity matrix consisting of MBPD1-3 fusion protein coupled to Sepharose CL4B. After sequential washes with phosphate buffered saline (PBS), and PBS containing 0.5 M sodium chloride, bound antibodies were eluted in 3.5 M $MgCl_2$, dialyzed in 20 mM ammonium bicarbonate, and lyophilized. For anti-peptide antibodies, each of two male New Zealand White rabbits were

map dominant epitopes within the D1 motif, and to identify epitopes spanning the C-terminus of D1 and the N-terminus D2. The D1-3 immunogen produced antibodies with a broad spectrum of epitope specificities (FIG. 10A). Most notable was the recognition of epitopes with clusters of acidic amino acids, defined by SFEEDTEEDKPKYE and SFEEDTEKDKPK, spanning residues 07-20 of the D1-motif ($D1_{7-20}$) and $D2_{7-18}$ respectively. Previous work has shown that synthetic peptides $D1_{1-18}$ and $D2_{1-18}$ do not interact with the N-terminal fragment of Fn (Huff *et al.* 1994). Therefore, this antibody preparation contains a significant population of antibodies specific for amino acid sequences that do not contribute to Fn-binding. There was also more variable recognition of several decapeptides spanning the sequence $D1_{17-38}$. In contrast, antibodies generated using GSTD1-3 as the immunogen exhibited a restricted specificity, predominantly recognizing three consecutive decapeptides spanning the amino acid sequence $D1_{21-34}$, QGGNIVDIDFDSVP (FIG. 10B). In a previous study, synthetic peptides representing amino acids $D2_{18-38}$ and $D3_{16-36}$ respectively bound the N-terminal fragment of Fn with an affinity comparable to the intact D2 and D3 motifs (Huff *et al.*, 1994). Therefore, the major epitopes recognized by this antibody preparation occur within an amino acid sequence that is critical to Fn-binding. Furthermore, this antibody preparation demonstrated little reactivity towards the clusters of acidic amino acids that were major epitopes for antibodies generated with D1-3 as an immunogen. Neither of the antibody preparations recognized epitopes within an amino acid sequence spanning the C-terminal eight amino acids of the D1 motif, and the first eight amino acids of the D2 motif. Therefore, there appears to be no significant epitopes consisting of amino acid sequences that span two individual motifs.

When assayed with a series of 15 decapeptides spanning the D3 motif (FIG. 11), antibodies obtained with the GSTD1-3 immunogen exhibited no appreciable recognition of these peptides, while antibodies obtained with the D1-3 immunogen recognized VDFEEDTLPKV, representing the C-terminal 11 amino acids of D3. The sequence FEEDT is observed within this 11 amino acid sequence, and also in the two major epitopes within the D1 and D2 motifs that are recognized by this antibody preparation. Therefore, the D1-3 immunogen appears to have

generated antibodies with a high specificity for clusters of acidic amino acids, most notably in the N-terminal halves of the D1 and D2 motifs that do not contribute to Fn-binding.

5.10.2.3 USE OF SYNTHETIC PEPTIDES TO GENERATE ABS OF DEFINED SPECIFICITY

The GSTD1-3 immunogen produced antibodies that were effective inhibitors at low concentrations, and exhibited a high specificity for QGGNIVDIDFDSVP, spanning the amino acid sequence $D1_{21-34}$. The sequence $D2_{21-34}$ of the D2 motif (HGGNIIDIDFDSVP) is nearly identical, suggesting that antibodies specific for these epitopes alone are responsible for the inhibition of Fn-binding to *S. aureus*. However, the inhibition of Fn-binding was incomplete, and these antibodies exhibited no reactivity towards the sequence QFGGHNSVDFEEDT, comprising amino acids 20-33 of the D3 motif ($D3_{20-33}$), and containing amino acids that are known to be critical for Fn-binding (McGavin *et al.*, 1993; McGavin *et al.*, 1991). To obtain antibodies specific for this sequence, rabbits were immunized with a synthetic peptide $D3_{20-33}$, synthesized with an N-terminal cysteine for coupling to maleimide activated KLH. Rabbits were also immunized with $D1_{21-34}$ coupled to maleimide activated BSA, representing the major epitope recognized by antibodies generated with the GSTD1-3 immunogen. Both anti-peptide antibody preparations recognized the recombinant D1-3 peptide. Although the $D1_{21-34}$ immunogen was coupled to BSA, inclusion of 0.1% BSA in the antibody dilution buffers was sufficient to eliminate interference from recognition of the BSA blocking reagent that was employed in the ELISA assay. Subsequently, IgG was purified from immune sera utilizing Protein A, and converted into $F(ab')_2$ fragments. The resulting $F(ab')_2$ fragments recognized FnBP purified from *S. aureus* strain Newman (FIG. 12), and a reduction in the ELISA response was observed in the presence of increasing concentrations of soluble competing Fn, such that recognition of FnBP was virtually eliminated at 50 µg/ml of soluble Fn-- Consistent with the recognition of epitopes containing amino acid sequences that are critical to Fn-binding, both $F(ab')_2$ preparations exhibited concentration-dependent inhibition of Fn-binding to *S. aureus*

⌐>SEQ ID NO: 103 (09/010,3

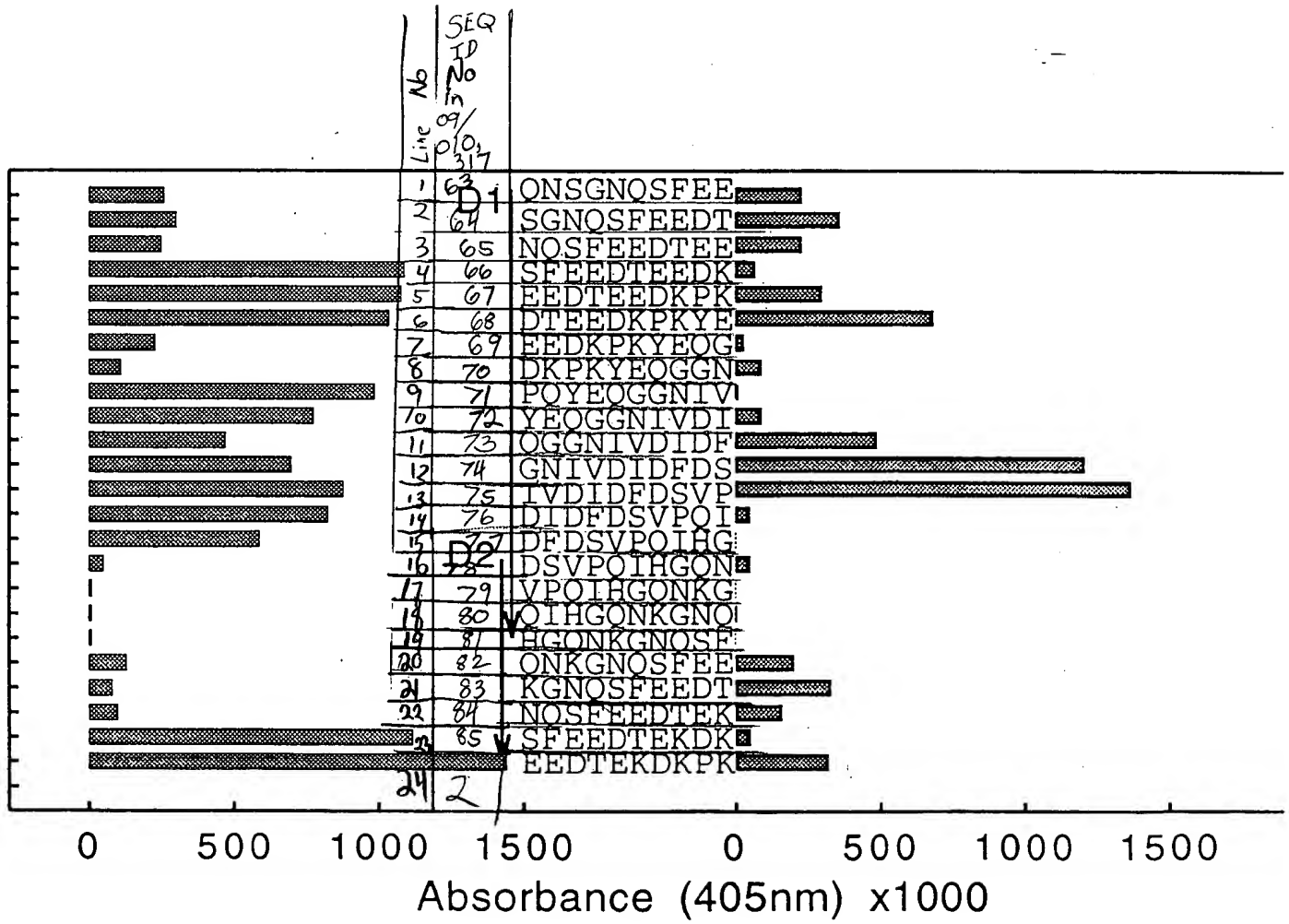

FIG. 10A

FIG. 10B

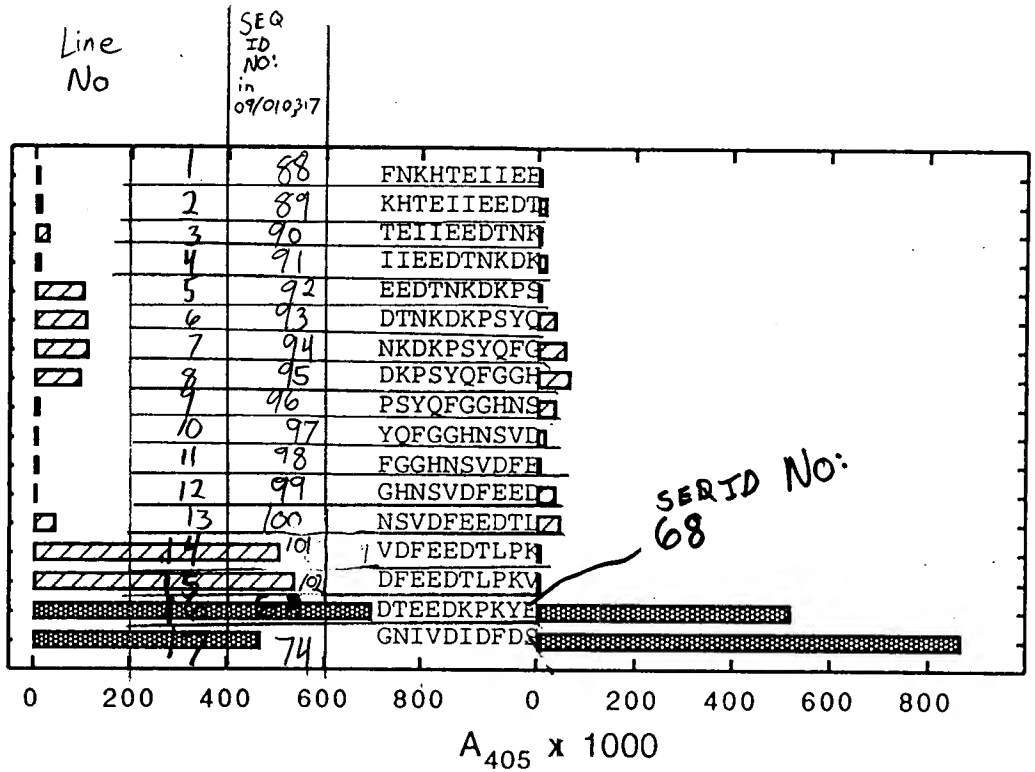

FIG. 11A

FIG. 11B